Remarks

Applicants' claims 94-116 are directed to a method of regulating intraocular pressure (IOP) by administering a pressure-modulating amount of a sodium-hydrogen exchanger inhibitor. Prior to Applicants' own work, there was no scientific proof for presuming that blockers of Na^+/H^+ exchange would by themselves lower IOP.

Claims 1, 38-55, 68, 92 and 93 have been cancelled and new claims 94-116 are presented. These claims are fully supported by the claims as filed and in the specification, for instance, at p. 3, lines 17-19 and 22-28, p. 6, lines 6-15 and 23-24, p. 8, lines 16-18, p. 14, lines 1-5 and lines 11-13, p. 14, line 29-p. 15, line 32, p. 18, lines 29-31 and p. 33, lines 4-6. No new matter has been added to the application.

Interview Summary

Applicants thank Examiner Jagoe for granting the personal interview held 27 October 2005. It is noted that the inventor's name is incorrectly listed as "Saito" on the Interview Summary. The correct name is "Civan."

During the interview, all of the pending claims were discussed in general. The possibility of limiting the modulators to exclude timolol was discussed. Burke *et al.* (USP 5, 215,991) was also discussed.

Information Disclosure Statement

The Examiner notes that copies of documents 64-67 and 69-77 on the Information Disclosure Statement filed 23 March 2004 were not scanned into the USPTO system and were, therefore, not available to her for consideration. We herewith provide a copy of the stamped postcard related to the submission of this Information Disclosure Statement to verify that these documents were previously submitted and, therefore, no fee is currently required for their resubmission. We again provide copies of documents 64-67 and 69-77, as well as another copy of the corresponding PTO-1449 for the Examiner's convenience. We respectfully request the Examiner to consider these references and to indicate the same on the copy of the PTO-1449.

Response to rejections

In view of the cancellation of previously pending claims, all of the pending rejections are rendered moot. In the interest of compact prosecution, however, the new claims are distinguished from the previously cited art as discussed below.

Re: Drug Facts and Comparisons, (1994) Wolters Kluwer Company, St. Louis, MO, pp. 2287-2292

This reference teaches the use of beta adrenergic blockers as therapeutics to reduce intraocular pressure. Beta adrenergic blockers, such as timolol, bind beta adrenergic receptors of the ciliary processes (specification, p. 4, lines 7-14). As discussed in the attached Declaration of Dr. Civan, who is the inventor who appeared at the Interview, beta adrenergic blockers are not generally considered sodium-hydrogen exchanger isoform (NHE) inhibitors by the ordinary skilled artisan. Therefore, although Drug Facts and Comparisons may mention the use of timolol, it makes no mention of NHE inhibitors and fails to teach or suggest NHE inhibitors as therapeutics to regulate intraocular pressure.

Timolol is not, and never has been recognized in the art as a NHE inhibitor, as can been seen from the two attached references listing known NHE inhibitors in 1999, at the time of the invention, and a more recent list dated2003. Although used for myocardial purposes, at the time of the invention, NHE inhibitors did not include timolol or any other beta blocker. For instance, Karmazyn discloses a variety of NHE inhibitors (*Ann. N.Y. Acad. Sci.* 874:326-334 (1999)). See pp. 326-327, bridging sentence. Karmazyn does not disclose or suggest timolol or any other beta blocker is an NHE inhibitor. Subsequent to the invention, NHE inhibitors still are not known to include beta blockers. For instance, Masereel *et al.* review numerous NHE inhibitors but do not teach or suggest beta blockers are NHE inhibitors (*Eur. J. Med. Chem.* 38:547-554 (2003)). Thus, the term "NHE inhibitors" does not refer to, or suggest, timolol or a beta blocker.

Since neither of the cited references represents art published prior to the filing date of the present invention, neither are currently submitted as such on an Information Disclosure Statement or form, although the references are attached hereto for the convenience of the Examiner. Should the Office feel that an IDS filing of these references, or any fee, is necessary, Applicants will be willing to comply if so notified.

Re: US Patent No. 5,215,991 to Burke ("Burke")

Burke teaches that amiloride and various amiloride analogs are by themselves inactive for lowering intraocular pressure. See col. 1, lines 56-61, col. 6, lines 62-65, Figures 1A-1C, col. 7, lines 17-19 and Tables V and VI. Burke demonstrates that NHE inhibitors are merely potentiaters of the pressure-regulating activity of alpha2 agonists. Burke's data and statements clearly indicate that NHE inhibitors are not pressure modulators. Thus, Burke cannot teach or suggest a pressure modulating amount of an NHE inhibitor. Consequently, Burke cannot teach or suggest a combination of a pressure-modulating amount of an NHE inhibitor with any other drug. Thus, the instant invention is not anticipated by Burke or made obvious in view of Burke and any other reference.

The Examiner stated on p. 9 of the August 11, 2005 office action that "if cariporide alone did not lower intraocular pressure in Burke, it is not clear to the examiner how cariporide would lower intraocular pressure in the instant case." It is believed that the Examiner meant to refer to "amiloride" since Burke is silent with regard to cariporide. While the Examiner may not understand how amiloride (or cariporide for that matter) lowers intraocular pressure in the instant case, the fact remains that the data as a whole presented in the instant specification demonstrate that this occurs. See, for instance, Example 3 and Figure 16. Furthermore, the data have been additionally confirmed by post-filing data generated by one of the inventors (Avila *et al., Invest. Ophthalmol. Vis. Sci.* 43:1897-1902 (2002)), previously provided to the Office.

In addition, as explained previously in the record (see, *e.g.*, p. 12 of Applicants' Response dated July 24, 2004), rabbits - the animals used by Burke - do not have a trabecular network in their eyes. While not wishing to be bound by theory, Applicants hypothesize that the shrinking of trabecular meshwork cells by the action of blockers of the sodium-hydrogen antiport enhances aqueous humor outflow, thereby reducing intraocular pressure. Rabbits, therefore, are not necessarily effective for the demonstration of the effect of an NHE inhibitor or other composition on animals having a trabecular network in their eyes, and cannot be predictive of results in the aqueous humor of the human eye. Thus, a difference in structure of the composition, combined with a difference in functional physiology of the test animal, may explain why Burke failed to observe pressure regulation by an NHE inhibitor.

Re: US Patent No. 6,348,476 to Scholtz *et al.* ("Scholtz")

Scholtz teaches benzoylguanidine compounds as NHE inhibitors and their use in combination with a cardiovascular medicament for cardiovascular therapies. Cariporide is disclosed as one such benzoylguanidine compound. Scholtz is, however, completely silent regarding intraocular pressure. Consequently, Scholtz cannot suggest that an NHE inhibitor can regulate intraocular pressure. As such, Scholtz cannot and does not anticipate the instant invention. Furthermore, Scholtz, in combination with any other reference, does not render obvious the instant invention.

In fact, if one were to rely upon the Burke patent with which the Examiner suggests that Scholtz *et al.* be combined, one of ordinary skill in the art would have understood that blockers of sodium-hydrogen exchange could not lower IOP. Thus, the deficiencies of Burke cannot be met by Scholtz *et al.* to teach Applicants' invention. Each cited reference fails to teach the independent use of a sodium-hydrogen exchange (NHE) inhibitor to reduce IOP. Thus, even when combined, they cannot, and do not, render Applicants' invention obvious.

In sum, Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendments or response, she is asked to contact Applicants' undersigned representative at (215) 988-3361.

Respectfully submitted,

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